REMARKS

Claims 1-26 are pending. Claims 22-26 remain pending, but are withdrawn from consideration as a non-elected invention under a restriction requirement.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider the rejections of the claims, that he withdraw same, and that he pass the application to issue.

Applicants' undersigned representative appreciates the courtesy by the Examiner for the interview held on May 13, 1999. This interview was very productive and useful in clarifying the grounds upon which the Office has rejected the claims of the present invention. Applicants in response provide the following comments herein below.

Rejection of the claims under 35 U.S.C. §112, first paragraph.

Claims 1-21 are rejection under 35 U.S.C. § 112, first paragraph as the claims are considered enabling only for those particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21 *et seq.* of the specification. Applicants respectfully traverse these rejections based upon the following remarks.

Applicants acknowledge with appreciation the Examiner's withdrawal of six of ten grounds of rejection of the claims under 35 U.S.C. §112, first paragraph. The Examiner has, however, maintained rejection of the claims on four grounds, which will each be addressed in turn.

1. Diverse peptides

The Examiner has maintained the rejection of the claims because the specification allegedly fails to provide an enabling disclosure commensurate in scope with the claims. The Examiner has cited Applicants' teaching that certain peptides inhibit CTL activity and certain ones do not. Specifically for example, the Examiner finds that the ordinary skilled artisan would

consider the diversity of peptides as claimed unpredictable and cites the differential activity between HLA-B2702 and HLA-B2705, where the former blocks CTL response, while the latter fails to do so.

Applicants respectfully point out that the passage in the specification cited and relied upon by the Office refers to the biological activity of monomers, not dimers as claimed. Further, this passage is directed to the biological activity of CTL lysis not inhibition of proliferation of lymphocytes as claimed. The attention of the Office is directed to page 24, line 13-25, whereat the dimer B2702.84-75/75-84 is disclosed to inhibit proliferation, but the monomers B2702.75-84 and B7.75-84 do not. This disclosure further teaches that the substitution of the B2702.84-75/75-84 in either or both of the Ile^{80} residues with Thr, does not result in the inhibition of proliferation of lymphocytes as does result from the non-substituted dimeric peptide. Similar data were obtained with the B2702.84-79/79-84, which provides further support for the functionality of the shorter sequence of aa 79-84.

The specification provides clear guidance to the skilled artisan, not ambiguous or contradictory teachings, that the claimed dimers inhibit proliferation of lymphocytes. In view of the assays presented, such as measuring a decrease in the incorporation of ^{3}H-thymidine as taught in Example 1, the skilled artisan would not be required to conduct undue experimentation to make and/or use the claimed invention.

2. Variants

The claims are rejected as requiring undue experimentation for reasons similar to those stated by the Examiner concerning "Diverse Peptides" as discussed *supra*. Again, Applicants respectfully maintain that the specification provides clear guidance to the skilled artisan as to the variations in amino acid sequence; how to screen for activity correlated to the amino acid sequence as well as which amino acids participate in promoting immunomodulating activity. Specifically, in view of the claimed sequence of aa 79-84, which through substitution at position

80 and as discussed above, appears to participate in the biological activity of these dimer peptides. The Examiner is respectfully requested to withdraw this ground of rejection.

3. Immunosuppressive agent

The Examiner has maintained this ground of rejection with regard to claim 18. The Examiner has further indicated that it would be helpful to provide evidence that the recited peptides alone would have activity in increasing allograft survival.

Applicants respectfully traverse this ground of rejection for the reasons of record and in view of the following additional comments. The present claim 18 is now limited to a therapeutically effective regimen, which the skilled artisan could easily identify following routine experimentation. Further, Applicants note that in the specification at page 35, lines 17-26, the use of the claimed peptides without an immunosuppressive agent clearly results in an extension of the period of acceptance of a transplant. While, the specification does teach that an improved outcome is expected by using both the claimed peptides and an immunosuppressive agent, there is clear guidance to the ordinary skilled artisan how to extend the period of acceptance of the transplant by using the claimed peptide in a therapeutically effective regimen. The Examiner is respectfully requested to withdraw this ground of rejection.

4. Homodimer/Heterodimer

Applicant traverses the Examiner's rejection of the claims as lacking enablement. Applicants respectfully traverse this rejection.

Further, Applicants note that the Examiner pointed out that Table 1, at page 21 of the specification only exemplifies the "beta-alpha" variety and not other dimeric forms. Applicants interpret what the Examiner intends to point out that Table 1 provides peptides of the formula $\alpha\beta$, where α is (b) and β is (a) (based upon the claimed formula:

(a) is $\{R\ aa^{76\text{-}77}\ L\}\ (aa^{79\text{-}84})$ or (b) is $(aa^{84\text{-}79})\ \{L\ aa^{77\text{-}76}\ R\}$).

That is, the Examiner considers that the dimers presented in Table 1 are only of the: (b)/(a) variety, where (b)=(aa^{84-79}) {L aa^{77-76} R} and (a)={R aa^{76-77} L} (aa^{79-84}).

However, Applicants further note that Table 1, actually provides the following dimer varieties: B2702.84-75/75-84 is actually: (b)/(a); and B2702.84-75/84-75 is actually: (b)/(b)

In the specification at page 22, line 9, the (a)/(a) dimer (B2702.75-84/75-84) is disclosed as having similar activity with regard to inhibiting lysis. Also, a number of dimers are presented with at least one amino acid substituted from the wildtype sequence.

The Examiner's suggestion that the claims are not enabled by the specification because only one allelic product (HLA-B2702) is taught is considered inaccurate. The Examiner is urged to review Example 2, beginning at page 26, whereat peptides of the B7 allele are also shown as having immunomodulating activity (e.g., see page 28, line 26; Table 4 at page .29; page 30, line 22).

Applicants respectfully urge that the specification clearly provides broader guidance than the Examiner suggested. The skilled artisan in following the specification would not require undue experimentation to identify which sequences possess lymphocyte immunomodulating activity in view of the several assays taught as well as the identification of amino acids critical to this activity. Applicants therefore request the Examiner to reconsider this ground of rejection and withdraw same.

Rejection of the claims under 35 U.S.C. §103(a).

Claims 1-21 are rejected under 35 U.S.C. § 103(a) as obvious over Olsson (US PN 5,073,540) or WO88/05784.

Each of Olsson and WO88/05784 teach peptide sequences relating to alleles of the MHC Class 1 antigens.

Applicants respectfully traverse this rejection in view of the following remarks. Neither of these references teaches nor suggests the presently claimed dimeric compounds, methods of using or method of genetic expression to make. These references fail to teach the significance of the claimed sequence of amino acids as well as the significance of creating dimers of these sequences, as presently claimed. Neither of the references teaches nor suggests the acylation of the N-terminal nor do either of the references teach amidation or esterification of the C-terminal regions. Also, neither of these references teaches nor suggests that the presently claimed dimers inhibit proliferation of lymphocytes.

The Examiner in response notes that "one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer." This is a surprising conclusion, since the Examiner has not pointed to any teaching of the reference or the art for support. In fact, the specification suggests the contrary. The disclosure, for example, at page 24, lines 15-17, teaches that the dimer B2702.84-75/75-84 inhibits proliferation of lymphocytes as measured by the decreased incorporation of ^{3}H-thymidine, but that the monomers B2702.75-84 and B7.75-84 do not. Applicants have noted that the Examiner would drop this rejection if the claims were limited to palindromic dimers, such as B2702.84-75/75-84. Applicants further point out that the B2702.75-84/75-84 is not a palindromic dimer, but yet it showed similar activity to the palindrome with regard to inhibiting lysis (See: the Specification at page 22, lines 8-9).

Applicants respectfully urge that neither alone nor together do Olsson and WO88/05784 teach or suggest the presently claimed compounds or methods of use.

Applicant respectfully submits that these rejections may be properly withdrawn and the claims found allowable. If the Examiner considers that a telephone interview would be helpful in furthering the prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number indicated below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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